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Exercise dose-response relationship with heart rate variability in individuals with overweight and obesity: Protocol for a systematic review and meta-analysis of randomized controlled trials

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Title: Exercise dose-response relationship with heart rate variability in individuals with overweight and obesity: Protocol for a systematic review and meta-analysis of randomized controlled trials

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Title: Exercise dose-response relationship with heart rate variability in individuals with overweight and obesity: Protocol for a systematic review and meta-analysis of randomized controlled trials

Abstract:

Objective: To estimate the extent to which exercise doses impacts on heart rate variability (HRV) among individuals living with overweight and obesity class I and II.

Methods: A systematic literature search will be performed using PubMed/Medline, Scopus, EMBASE, ProQuest, CINAHL, Web of Science, and the Cochrane Library for articles dating from 1965 to December 2020. Studies with parallel randomized control trials (RCTs), enrolled adolescent and adult individuals with overweight [BMI ≥ 25 – ≤ 29.9] and obesity [class I BMI: 30 - 34.9 and class II BMI: 35 - 39.9] undergoing aerobic or resistance training or concurrent exercise training are inclusion requirements. For data synthesis, sensitivity analysis, subgroup analysis, and risk of bias assessment, Stata V.13.0 software will be used.

Key words: cardiac autonomic function, heart rate variability, exercise training, aerobic exercise, resistance exercise, concurrent exercise, physical activity

PROSPERO Registry no: CRD42019104154

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3 55 **Strength and limitation:**
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6 56 ▪ This research will evaluate the impact of exercise (aerobic, resistance, and
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9 57 concurrent training) on HRV in overweight [BMI ≥ 25 to ≤29.9] and obesity [class I
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11 58 BMI: 30 - 34.9 and class II BMI: 35 - 39.9] Uniqueness of this study is focusing on the
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13 59 dose-response analysis of intervention
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16 60 ▪ Two reviewers will perform data extraction and risk of bias evaluation separately
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19 61 ▪ There may be a language bias, as only English language article will be included
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22 62 **Introduction:**
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25 63 Over the past 35 years, the global prevalence of obesity has tripled and is expected to rise
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27 64 by over one billion people by 2030 as per the current trend.¹⁻² Individuals living with obesity
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29 65 have a significantly high risk of developing cardiovascular disease, diabetes, hypertension,
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31 66 cancer, stroke, and chronic disease, including osteoarthritis.¹ Obesity has also been linked to
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33 67 alteration in cardiac autonomic activity as seen when measuring heart rate variability
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35 68 (HRV).³⁻⁴ Heart rate variability is a non-invasive technique for analyzing autonomic
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37 69 function by measuring beat-to-beat changes in R-R intervals.⁵ Low HRV is associated with
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39 70 higher skinfold thickness, higher body mass index (BMI), higher body fat percentages and is
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41 71 an autonomous predictor of cardiovascular mortality and sudden cardiac death.⁶⁻⁸ In
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43 72 contrast, higher HRV is found to be associated with reduced morbidity, mortality, improved
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45 73 quality of life, and psychological well-being.⁹⁻¹¹
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52 74 Earlier studies have reported that obese individuals are relatively more susceptible to
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54 75 ventricular arrhythmias, which in turn was found to be a powerful indicator of sudden
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56 76 death.¹²⁻¹⁵ Several researchers have shown decreased HRV in obese people (BMI ≥30) and
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59 77 this suggests that autonomic disturbances could be involved in the processes stimulating
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3 78 arrhythmia in such people.¹⁶⁻¹⁸ Weight loss by exercise training and dietary intervention, on
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6 79 the other hand, has been shown to reverse the detrimental impact of weight gain on
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8 80 autonomic function.^{6-7,18-19}
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11 81 Benefits of exercise training are documented as a possible non-pharmacological weight-loss
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13 82 approach.^{20,21} Exercise in terms of aerobic, resistance, or concurrent are the efficacious
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16 83 means to improve anthropometric indicators of adiposity.²²⁻²⁴ These exercise types are
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18 84 characterized by multiple sub-divisions such as frequency, intensity, and volume of exercise
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21 85 that may be considered to constitute the exercise “dosage.” The effectiveness of the
22
23 86 exercise intervention in reducing body weight is documented as dose-dependent and it is
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26 87 mediated by autonomic control.²⁵⁻²⁹
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29 88 Current evidence on the influence of long-term exercise training on HRV in healthy or obese
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31 89 individuals is inconsistent, with several studies showing significant increase in the HRV
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34 90 following an exercise training with varying dose ranging from 3 weeks to 12 months of
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36 91 exercise training in healthy and obese individuals^{7,19,30-33} while other studies did not show
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38 92 such an effect.³⁴⁻³⁶ Such differences in effect may be due to either participant attributes, a
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41 93 technique of measurement to estimate HRV, study design, exercise types, and/or exercise
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44 94 dose parameter.³⁶
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47 95 A meta-analysis study²⁹ in a healthy person over 18 years of age suggested that aerobic
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49 96 exercise training can make substantial improvements in the RR interval, and the effect size
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52 97 for changes in the RR interval recorded in this study was significantly higher in long exercise
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54 98 interventions (>12 weeks) than in shorter treatments (<12 weeks). Also, a meta-analysis in
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56 99 elderly³⁷ suggested endurance-type exercise is effective for increasing HRV, and exercise
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59 100 frequency appears to be a powerful component of training that decides HRV improvement.
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A recent meta-analysis¹⁹ reported improvement in HRV following weight-loss strategies such as dietary approaches, aerobic training, strength training, and exercise programs coupled with dietary approaches. Also, they suggested that the impact of weight loss on the ANS might depend primarily on the amount of weight loss. Differences in the dosage of exercise, such as the duration, frequency, and strength of exercise training, are considered to be responsible for the degree of improvement in autonomic cardiac function and the change in body weight.¹⁹

The exercise-based weight loss program is known to be part of the key therapy for obesity and recognizing its impact on the HRV will be value-added to the current evidence. In addition, no studies to date have comprehensively analyzed and examined the evidence of exercise dose-response on HRV in people with overweight or obesity. Therefore, the objective of this review is to estimate the extent to which exercise-dose increases heart rate variability in individuals living with overweight and obesity class I and II.

METHODS:

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines are used for the current study.³⁸ This systematic review will consider only randomized controlled trials (RCTs). This systematic review is registered with PROSPERO (CRD42019104154). Any amendments to this study protocol will be reported.

Electronic Search:

Seven databases will be searched PubMed/Medline, Scopus, EMBASE, ProQuest, CINAHL, Web of Science, and the Cochrane Library, for articles dating from 1965 to December 2020, since Hon and lee⁵ published their understanding of the clinical importance of heart rate

123 variability in 1965. We will also refer to The ClinicalTrials.gov, the International Clinical Trial
 124 Registry Platform of the WHO's, the reference list of key articles identified via Scopus, and
 125 articles that cited the included articles. Also, authors will be contacted to get aggregate
 126 study data that has been completed but not published. If more than one publication
 127 describes the same study, the one that provides the most data will be included in the meta-
 128 analysis. Studies will be limited to publications in the English language. The search will be
 129 carried out by the first author and a medical librarian. Table 1 Shows the search strategy for
 130 PubMed.

131 **Table 1 Shows the search strategy for PubMed**

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((((((((((((("exercise"[MeSH Terms]) OR exercise ) OR exercise[Text Word]) OR
exercise[Title]) OR exercise[Title/Abstract])) OR (((aerobic exercise) OR aerobic
exercise[Text Word]) OR aerobic exercise[Title]) OR aerobic exercise[Title/Abstract])) OR
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OR resistance exercise[Title/Abstract])) OR (((concurrent exercise) OR concurrent
exercise[Text Word]) OR concurrent exercise[Title]) OR concurrent
exercise[Title/Abstract])) OR (((combination exercise) OR combination exercise[Text
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training) OR aerobic training[Text Word]) OR aerobic training[Title]) OR aerobic
training[Title/Abstract])) exercise dose OR dose response OR aerobic dose OR resistance
dose OR concurrent dose OR combination dose OR (((("cardiorespiratory fitness"[MeSH
Terms]) OR cardiorespiratory fitness[Text Word]) OR cardiorespiratory fitness[Title]) OR
  
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cardiorespiratory fitness[Title/Abstract]) OR cardiorespiratory fitness)) OR (((physical activity) OR physical activity[Text Word]) OR physical activity[Title]) OR physical activity[Title/Abstract])) OR (((cardiorespiratory endurance) OR cardiorespiratory endurance[Text Word]) OR cardiorespiratory endurance[Title]) OR cardiorespiratory endurance[Title/Abstract])) OR (((strength training) OR strength training[Text Word]) OR strength training[Title]) OR strength training[Title/Abstract])) OR (((strengthening) OR strengthening[Text Word]) OR strengthening[Title]) OR strengthening[Title/Abstract])) AND

(((((("overweight"[MeSH Terms]) OR overweight) OR overweight[Text Word]) OR overweight[Title]) OR overweight[Title/Abstract])) OR (((("obesity"[MeSH Terms]) OR obesity) OR obesity[Text Word]) OR obesity[Title]) OR obesity[Title/Abstract])) OR (((healthy individuals[Text Word]) OR healthy individuals[Title]) OR healthy individuals[Title/Abstract]) OR healthy individuals)))

AND

(((((((((heart rate variability) OR heart rate variability[Text Word]) OR heart rate variability[Title]) OR heart rate variability[Title/Abstract])) OR (((autonomic function) OR autonomic function[Text Word]) OR autonomic function[Title]) OR autonomic function[Title/Abstract])) OR (((sympathetic function) OR sympathetic function[Text Word]) OR sympathetic function[Title]) OR sympathetic function[Title/Abstract])) OR (((parasympathetic function) OR parasympathetic function[Text Word]) OR parasympathetic function[Title]) OR parasympathetic function[Title/Abstract])) OR (((vagal function) OR vagal function[Text Word]) OR vagal function[Title]) OR vagal function[Title/Abstract]))

Eligibility Criteria and Study selection:

The titles and abstracts screening will be done for eligibility and the article considered appropriate will be reviewed in full-text papers. This process will be conducted using Covidence (www.covidence.org).³⁹

Inclusion Criteria:

Studies will be included if a) Parallel randomized control trials (RCTs), b) enrolled adolescent (Age ≥ 10 years) and adult individuals with overweight [BMI ≥ 25 – ≤ 29.9] and obesity [class I BMI: 30 - 34.9 and class II BMI: 35 - 39.9] undergoing aerobic or resistance exercise training or concurrent exercise training (Table 2)⁴⁰

Table 2: Operational definitions of exercises type used for the current systematic review according to The American College of Sports Medicine.⁴⁰

Exercise Type	Operational definition
Aerobic/endurance exercise training-	Aerobic exercise as any activity that uses large muscle groups, can be maintained continuously and is rhythmic in nature
Resistance/strength exercise training	Strength training that involves the performance of physical exercises which are designed to improve muscle strength and endurance
Concurrent exercise training	The combination of muscle strength and aerobic exercise during the same session or training program

and had an outcome of interest as HRV c) exercise intervention is reported in terms of frequency, intensity, time, and type, and d) measurement of at least one variable of HRV before and after the training intervention is reported.

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Exclusion Criteria:

Exclusion criteria will be a) observational studies, b) studies measuring acute exercise effects, c) obesity class III (BMI ≥ 40) as it has been found that individuals living with severe obesity may have impaired autonomic function and this would confound the outcome of interest, and d) studies including individuals with cardiac, neurodegenerative, kidney or metabolic disease as they have an impact on autonomic function.^{37,41-42}

Study Selection:

Following different database searches, retrieved articles will be imported to Covidence platform³⁹ where the results will be combined and duplicates will be removed. As a large number of papers are expected to do the screening, four authors will be involved in the screening and pilot-tested on the first 10 % of titles and abstracts for the eligibility criteria. To harmonize the screening process, a training session will be provided to all reviewers. During this session reviewer will be asked to pilot-screen 15 titles/abstracts to prompt clarifications and screening decisions will be taken in compliance with inclusion/exclusion criteria. After scanning for titles and abstracts, articles that do not meet the inclusion requirements will be excluded and the remaining articles will have their full-text versions retrieved. The full-text screening will be done by two lead members of the synthesis team using the level of agreement between reviewers. Kappa statistics will be used to test the agreement [i.e. thresholds: <0.20 slight agreement, 0.21 - 0.40 fair agreement, 0.41 - 0.60 moderate agreement, 0.61 - 0.80 substantial agreement and >0.80 almost perfect agreement].⁴³ Disputes will be settled by agreement with the reviewers or by contacting an adjudicator. In a PRISMA flow chart, the study selection process is displayed.⁴⁴(Figure I)

171 Data extraction and analysis:

172 Outcomes:

173 In this study, the primary outcome of interest is the time domain (SDNN, SDANN, RMSSD,
174 pNN50) and frequency domain variables of HRV (Total power, VLF, LF, HF, LF/HF ratio).
175 (Table 3)

176 **Table 3: Heart rate variability Domains.⁵**

Time domain measures of HRV: Variable(units) and description	
SDNN (ms)	Standard deviation of all NN intervals
SDANN (ms)	Standard deviation of the averages of NN intervals
RMSSD (ms)	The square root of the mean of the sum of the squares of differences between adjacent NN intervals
pNN50 %	NN50 count divided by the total number of all NN intervals
Frequency domain measures of HRV: Variable(units) and description	
Total power ms ²	The variation of NN intervals over the temporal segment
VLF (ms ²)	Power in very low frequency range
LF (ms ²)	Power in low frequency range
HF (ms ²)	Power in high frequency range
LF/HF ratio	Ratio of LF and HF

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179 Cardiorespiratory endurance, muscular strength, adiposity/anthropometric measures are
180 the secondary outcome of interest. These outcomes are chosen based on the previous
181 research.^{7,19,30-33} If data are available in qualifying studies, the relationship of exercise
182 training with other endpoints, such as time effect and interaction effect with

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sociodemographic variables, anthropometric measures, presence of cardiovascular risk factors, diet, exercise adherence, and life stress, will also be analyzed.

Data extraction:

A data extraction form will be adopted from published literature.⁴⁵⁻⁴⁷ Data extraction process consists of manuscript title, author, time of publication, source of literature, characteristics of the trial (author, conducted/ publication year, duration, place of the trial conducted, number of participating centers, study design), the participants (sample size, participants randomized and patients analyzed in each group, age, sex, socioeconomic status, height, weight, body mass index, waist circumference, waist-hip ratio, waist-height ratio, and body fat percent), intervention (aerobic, resistance, and concurrent exercise dose in terms of frequency, intensity, number of sessions, duration, and progression), control group treatment, method of randomization, method of allocation, blinding process, outcome time point and follow- up period, lack of follow-up or withdrawal, any incidental findings reported and the main outcome measurement heart rate variability reported either in absolute or log transformed or both. Two independent reviewers will be pilot-testing the data extraction form and to resolve any disagreements team meetings will be conducted to refine the form. The two reviewers will perform data extraction separately. A training session will be held to harmonize the extraction of data, and at least two pilot extractions will be carried out to ensure accuracy. A written 'Data Extraction Guide' with detailed instructions will also be provided to reviewers. To assure accuracy, one lead member of the systematic review team will extract data from each article. An impartial third reviewer will cross-check the data extracted in duplicate. Inconsistencies in the data obtained will be resolved by agreement between the reviewers after reviewing the full-text article. When

discrepancies occur, an adjudicator will be contacted. If the data published is incomplete or vague, the authors of the research will be contacted. Data extraction will be independently cross-checked.

Quality and Risk of bias assessment:

Two reviewers will independently review each selected article to eliminate bias. All selected articles will be evaluated for their quality based on the Cochrane Collaboration's Risk of Bias Tool 2.0 (RoB 2.0)⁴⁸ for risk of bias assessment across five domains. Assessments will be carried out using an iterative online form available.⁴⁹ The domain of missing outcome data will be evaluated, as per Akobeng and Ebrahim.⁵⁰⁻⁵¹ For each domain, the probability of bias will be evaluated as 'low risk', 'some concerns', or 'high risk'. If at least one area is listed as 'high risk,' studies will be deemed to have an overall high risk of bias. Quality of evidence will be measured using the GRADE rating system.⁵² Publication bias will be evaluated using visual inspection of funnel plot asymmetry.⁵³

Data synthesis Strategy: Meta-analysis:

We will primarily examine the training effect (aerobic, resistance, and concurrent exercise training) on HRV. We will also explore possible sources of heterogeneity among studies by examining aerobic, resistance, and concurrent exercise impact with time point. To attain the standardized mean difference and 95% confidence interval, the data of interest given as continuous will be used for meta-analysis. The Q-statistic and I^2 tests will be used to test for heterogeneity between the included studies. Heterogeneity will be considered low if I^2 is \leq 40%, and high if I^2 is \geq 75%. We will use a random-effects model for meta-analysis if

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228 substantial heterogeneity ($I^2 > 40\%$) or fixed effects for homogeneous effects ($I^2 < 40\%$).⁵⁴
229 Aggregate data obtained from the included studies will be used for quantitative synthesis.
230 By plotting the data on a forest plot, heterogeneity will be evaluated visually.⁵⁵

231 **Analysis of subgroups or subsets:**

232 The sub-analysis will include baseline participant characteristics and exercise intervention
233 characteristics. Interaction effects between variables will be identified for subgroup
234 analysis.⁵⁵

235 **Significance:**

236 Due to modernization and mechanization of lifestyle, there is an increase in overweight and
237 obesity globally. Exercise is a key element to prevent lifestyle disease, therefore it is
238 important to explore dose-response benefits specifically towards heart rate variability to
239 maximize the physiological benefits. The study would help to understand the autonomic
240 response of the heart (i.e., heart rate variability) at different doses of exercise training. Also
241 can help to recommend the training regimen for overweight and obese people for optimum
242 gain in heart rate variability

243 **Ethics and dissemination:**

244 This review will not require an ethical authorization, since participant privacy issues do not
245 exist. Our results will provide data on the various forms of exercise dose-response on the
246 HRV in overweight and obese people. The results of this study will be published in a peer-
247 reviewed international journal, displayed at relevant conferences, and disseminated to
248 obesity-focused public organizations.

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Contributors:

All the authors conceived the idea for this systematic review and developed the protocol, drafted the manuscript, revised the manuscript for important intellectual content, and drafted the final version systematic review protocol manuscript for submission. All the contributors read and approved the final manuscript.

Funding: none**Competing interests:** None**Patient consent for publication:** not required**Availability of data and materials:** For this study, data sharing is not applicable.**References:**

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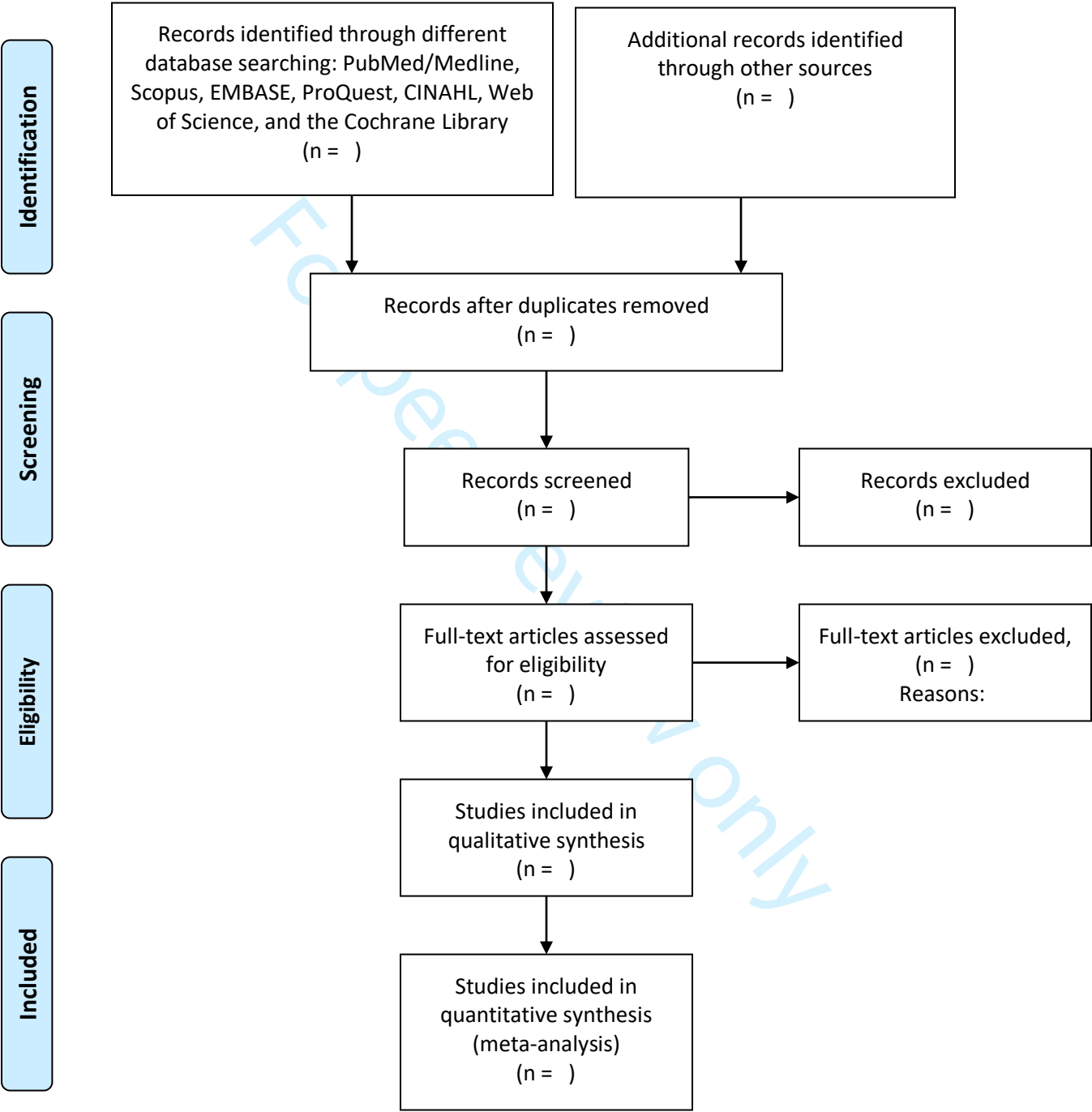
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For peer review only



Figure 1: Flow diagram for study selection based on the PRISMA guidelines: (Moher, Liberati, Tetzlaff, & Altman, 2009)



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Reporting checklist for protocol of a systematic review.

Title: Exercise dose-response relationship with heart rate variability in individuals with overweight and obesity: Protocol for a systematic review and meta-analysis of randomized controlled trials

Based on the PRISMA-P guidelines.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	NA
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1 & 2
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	14
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important	NA

protocol amendments

Sources	#5a	Indicate sources of financial or other support for the review	14
Sponsor	#5b	Provide name for the review funder and / or sponsor	NA
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	NA
Rationale	#6	Describe the rationale for the review in the context of what is already known	3-5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5-9
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5-9
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5-7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9-10
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10-12
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	10-11

1	Outcomes and	#13	List and define all outcomes for which data will be sought,	10-11
2	prioritization		including prioritization of main and additional outcomes, with	
3			rationale	
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6	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of	12
7	individual studies		individual studies, including whether this will be done at the	
8			outcome or study level, or both; state how this information will	
9			be used in data synthesis	
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13	Data synthesis	#15a	Describe criteria under which study data will be quantitatively	12-13
14			synthesized	
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17		#15b	If data are appropriate for quantitative synthesis, describe	12-13
18			planned summary measures, methods of handling data and	
19			methods of combining data from studies, including any	
20			planned exploration of consistency (such as I ² , Kendall's τ)	
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24		#15c	Describe any proposed additional analyses (such as	13
25			sensitivity or subgroup analyses, meta-regression)	
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28		#15d	If quantitative synthesis is not appropriate, describe the type	12-13
29			of summary planned	
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31	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as	12
32			publication bias across studies, selective reporting within	
33			studies)	
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37	Confidence in	#17	Describe how the strength of the body of evidence will be	12
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BMJ Open

Exercise dose-response relationship with heart rate variability in individuals with overweight and obesity: Protocol for a systematic review and meta-analysis of randomized controlled trials

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Keywords:	Lipid disorders < DIABETES & ENDOCRINOLOGY, REHABILITATION MEDICINE, General endocrinology < DIABETES & ENDOCRINOLOGY

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Title: Exercise dose-response relationship with heart rate variability in individuals with overweight and obesity: Protocol for a systematic review and meta-analysis of randomized controlled trials

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Title: Exercise dose-response relationship with heart rate variability in individuals with overweight and obesity: Protocol for a systematic review and meta-analysis of randomized controlled trials

Abstract:

Objective: To estimate the extent to which exercise doses impacts on heart rate variability (HRV) among individuals living with overweight and obesity class I and II.

Methods: A systematic literature search will be performed using PubMed/Medline, Scopus, EMBASE, ProQuest, CINAHL, Web of Science, and the Cochrane Library for articles dating from 1965 to December 2020. Inclusion criteria include studies designed as parallel-arm randomized trials, enrolling adolescent and adult individuals with overweight [BMI ≥ 25 – ≤ 29.9] and obesity [class I BMI: 30 - 34.9 and class II BMI: 35 - 39.9] undergoing aerobic or resistance training or concurrent exercise training. For data synthesis, sensitivity analysis, subgroup analysis, and risk of bias assessment, Stata V.13.0 software will be used.

Key words: cardiac autonomic function, heart rate variability, exercise training, aerobic exercise, resistance exercise, concurrent exercise, physical activity

PROSPERO Registry no: CRD42019104154

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Strength and limitation:

- Strength of the design is the focus on dose-response analysis of intervention
- Two reviewers will perform data extraction and risk of bias evaluation separately
- Only English language article will be included

Introduction:

Over the past 35 years, the global prevalence of obesity has tripled and current trends, if extrapolated would lead to approximately over one billion people by 2030.¹⁻² Individuals living with obesity have a significantly higher risk of developing cardiovascular disease, diabetes, hypertension, cancer, stroke, and chronic disease, including osteoarthritis.¹ Obesity has also been linked to alteration in cardiac autonomic activity as seen when measuring heart rate variability (HRV).³⁻⁴ Heart rate variability is a non-invasive technique for analyzing autonomic function by measuring beat-to-beat changes in R-R intervals of electrocardiogram (ECG) signals.⁵ Low HRV is associated with higher skinfold thickness, higher body mass index (BMI), higher body fat percentages and is an autonomous predictor of cardiovascular mortality and sudden cardiac death.⁶⁻⁸ In contrast, higher HRV is found to be associated with reduced morbidity, mortality, improved quality of life, and psychological well-being.⁹⁻¹¹

Earlier studies have reported that obese individuals are relatively more susceptible to ventricular arrhythmias, which has been found to be a powerful indicator of sudden death.¹²⁻¹⁵ Several researchers have shown decreased HRV in obese people (BMI ≥30) and this suggests that autonomic disturbances could be involved in the processes stimulating arrhythmia in such people.¹⁶⁻¹⁸ Weight loss by exercise training and dietary intervention, on

the other hand, has been shown to reverse the detrimental impact of weight gain on autonomic function.^{6-7,18-19}

Benefits of exercise training are documented as a possible non-pharmacological weight-loss approach.^{20,21} All forms of exercise, whether aerobic, resistance, or combination of aerobic and resistance (concurrent), are effective methods of improving anthropometric indicators of adiposity.²²⁻²⁴ These exercise types are characterized by multiple sub-divisions such as frequency, intensity, and volume of exercise that may be considered to constitute the exercise “dosage.” The effectiveness of the exercise intervention in reducing body weight is documented as dose-dependent and it is mediated by autonomic control.²⁵⁻²⁹

Current evidence on the influence of long-term exercise training on HRV in healthy or obese individuals is inconsistent, with several studies showing significant increase in the HRV following an exercise training with varying dose ranging from 3 weeks to 12 months of exercise training in healthy and obese individuals^{7,19,30-33} while other studies did not show such an effect.³⁴⁻³⁶ Such differences in effect may be due to either participant attributes, a technique of measurement to estimate HRV, study design, exercise types, and/or exercise dose parameter.³⁶

A meta-analysis done using data from studies carried out in healthy people suggested that aerobic exercise training can make substantial improvements in the RR interval, and the effect size for changes in the RR interval recorded in this study was significantly higher in long exercise interventions (>12 weeks) than in shorter treatments (<12 weeks).²⁹ Meta-analysis including studies done in the elderly³⁷ suggested endurance-type exercise is effective for increasing HRV, and exercise frequency appears to be a powerful component of training that leads to HRV improvement.

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3 99 A recent meta-analysis¹⁹ reported improvement in HRV following weight-loss strategies such
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6 100 as dietary approaches, aerobic training, strength training, and exercise programs coupled
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8 101 with dietary approaches. Also, this study suggested that the impact of weight loss on the
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12 103 exercise, such as the duration, frequency, and strength of exercise training, are considered
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14 104 to be responsible for the degree of improvement in autonomic cardiac function and the
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16 105 change in body weight.¹⁹
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21 106 The Exercise-based weight loss programs are known to be a key part of therapy for obesity
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23 107 and evaluating its impact on HRV would add value to current assessments of the evidence
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25 108 base. In addition, no studies to date have comprehensively analyzed and examined the
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27 109 evidence of exercise dose-response on HRV in people with overweight or obesity. Therefore,
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29 110 the objective of this review is to estimate the extent to which exercise-dose increases heart
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31 111 rate variability in individuals living with overweight and obesity class I and II.
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36 112 **METHODS:**

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39 113 The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-
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41 114 P) guidelines are used for the current study. PRISMA will be used to assist reporting of the
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43 115 SR, once completed.³⁸ This systematic review will consider only randomized controlled trials
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45 116 (RCTs). This systematic review is registered with PROSPERO (CRD42019104154). Any
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47 117 amendments to this study protocol will be reported.
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52 118 **Electronic Search:**

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57 120 Web of Science, and the Cochrane Library, for articles dating from 1965 to December 2020,
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121 since Hon and Lee⁵ published their understanding of the clinical importance of heart rate
 122 variability in 1965. We will also refer to clinicaltrials.gov, the World Health Organization's
 123 registry platform ICTRP, the reference lists of key articles identified via Scopus, and articles
 124 that cited the included articles. Also, authors will be contacted to obtain for studies that
 125 have been completed but not published. If more than one publication describes the same
 126 study, the one that provides the most data will be included in the meta-analysis. Studies will
 127 be limited to publications in the English language. The search will be carried out by the first
 128 author and a medical librarian. Table 1 Shows the search strategy for PubMed.

129 **Table 1 Shows the search strategy for PubMed**

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exercise[Title]) OR exercise[Title/Abstract])) OR (((aerobic exercise) OR aerobic
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(((((((((heart rate variability) OR heart rate variability[Text Word]) OR heart rate variability[Title]) OR heart rate variability[Title/Abstract])) OR (((autonomic function) OR autonomic function[Text Word]) OR autonomic function[Title]) OR autonomic function[Title/Abstract])) OR (((sympathetic function) OR sympathetic function[Text Word]) OR sympathetic function[Title]) OR sympathetic function[Title/Abstract])) OR (((parasympathetic function) OR parasympathetic function[Text Word]) OR parasympathetic function[Title]) OR parasympathetic function[Title/Abstract])) OR (((vagal function) OR vagal function[Text Word]) OR vagal function[Title]) OR vagal function[Title/Abstract]))

131 Eligibility Criteria and Study selection:

132 The titles and abstracts screening will be done for eligibility and the article considered
 133 appropriate will be reviewed in full-text papers. This process will be conducted using
 134 Covidence (www.covidence.org)³⁹ and it is expected to be completed by December 2021.

135 Inclusion Criteria:

136 Studies will be included if they report data from a) parallel-arm randomized trials (RCTs), b)
 137 enrolled adolescent (Age \geq 10 years) and adult individuals with overweight [BMI \geq 25 – \leq 29.9]
 138 and obesity [class I BMI: 30 - 34.9 and class II BMI: 35 - 39.9] undergoing aerobic or
 139 resistance exercise training or concurrent exercise training (Table 2)⁴⁰

140 **Table 2:** Operational definitions of exercises type used for the current systematic review
 141 according to The American College of Sports Medicine. ⁴⁰

Exercise Type	Operational definition
Aerobic/endurance exercise training-	Aerobic exercise as any activity that uses large muscle groups, can be maintained continuously and is rhythmic in nature
Resistance/strength exercise training	Strength training that involves the performance of physical exercises which are designed to improve muscle strength and endurance
Concurrent exercise training	The combination of muscle strength and aerobic exercise during the same session or training program

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 143 and had an outcome of interest as HRV c) exercise intervention is reported in terms of
 144 frequency, intensity, time, and type, and d) measurement of at least one variable of HRV
 145 before and after the training intervention is reported.

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Exclusion Criteria:

Exclusion criteria will be a) observational studies, b) studies measuring acute exercise effects, c) obesity class III (BMI ≥ 40) as it has been found that individuals living with severe obesity may have impaired autonomic function and this would confound the outcome of interest, and d) studies including individuals with cardiac, neurodegenerative, kidney or metabolic disease as they have an impact on autonomic function.^{37,41-42}

Study Selection:

Following different database searches, retrieved articles will be imported to the Covidence platform³⁹ where the results will be combined and duplicates will be removed. As a large number of papers are expected to require screening, four authors will be involved in screening. These authors will also perform pilot-testing of eligibility criteria on the first 10% of titles and abstracts. To harmonize the screening process, a training session will be provided to all reviewers. During this session reviewer will be asked to pilot-screen 15 titles/abstracts to prompt clarifications and screening decisions will be taken in compliance with inclusion/exclusion criteria. After scanning for titles and abstracts, articles that do not meet the inclusion requirements will be excluded and the remaining articles will have their full-text versions retrieved. The full-text screening will be done by two lead members of the synthesis team using the level of agreement between reviewers. Kappa statistics will be used to test the agreement [i.e. thresholds: <0.20 slight agreement, 0.21 - 0.40 fair agreement, 0.41 - 0.60 moderate agreement, 0.61 - 0.80 substantial agreement and >0.80 almost perfect agreement].⁴³ Disputes will be settled by agreement with the reviewers or by contacting an adjudicator. In a PRISMA flow chart, the study selection process is displayed.⁴⁴(Figure I)

169 Data extraction and analysis:

170 Outcomes:

171 In this study, the primary outcome of interest is the time domain (SDNN, SDANN, RMSSD,
172 pNN50) and frequency domain variables of HRV (Total power, VLF, LF, HF, LF/HF ratio).
173 (Table 3)

174 **Table 3: Heart rate variability Domains.⁵**

Time domain measures of HRV: Variable(units) and description	
SDNN (ms)	Standard deviation of all NN intervals
SDANN (ms)	Standard deviation of the averages of NN intervals
RMSSD (ms)	The square root of the mean of the sum of the squares of differences between adjacent NN intervals
pNN50 %	NN50 count divided by the total number of all NN intervals
Frequency domain measures of HRV: Variable(units) and description	
Total power ms ²	The variation of NN intervals over the temporal segment
VLF (ms ²)	Power in very low frequency range
LF (ms ²)	Power in low frequency range
HF (ms ²)	Power in high frequency range
LF/HF ratio	Ratio of LF and HF

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177 Secondary outcomes include Cardiorespiratory endurance, muscular strength,
178 adiposity/anthropometric measures. These outcomes are chosen based on the previous
179 research.^{7,19,30-33} If data are available in qualifying studies, the relationship of exercise
180 training with other endpoints, such as time effect and interaction effect with

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sociodemographic variables, anthropometric measures, presence of cardiovascular risk factors, diet, exercise adherence, and life stress, will also be analyzed.

Data extraction:

A data extraction form will be adopted from published literature.⁴⁵⁻⁴⁷ Data extraction process consists of manuscript title, author, time of publication, source of literature, characteristics of the trial (author, conducted/ publication year, duration, place of the trial conducted, number of participating centers, study design), the participants (sample size, participants randomized and patients analyzed in each group, age, sex, socioeconomic status, height, weight, body mass index, waist circumference, waist-hip ratio, waist-height ratio, and body fat percent), intervention (aerobic, resistance, and concurrent exercise dose in terms of frequency, intensity, number of sessions, duration, and progression), control group treatment, method of randomization, method of allocation, blinding process, outcome time point and follow- up period, lack of follow-up or withdrawal, any incidental findings reported and the main outcome measurement heart rate variability reported either in absolute or log transformed or both. Two independent reviewers will pilot test the data extraction form and to resolve any disagreements team meetings will be conducted to refine the form. The two reviewers will perform data extraction separately. A training session will be held to harmonize the extraction of data, and at least two pilot extractions will be carried out to ensure accuracy. A written 'Data Extraction Guide' with detailed instructions will also be provided to reviewers. To assure accuracy, one lead member of the systematic review team will extract data from each article. An impartial third reviewer will cross-check the data extracted in duplicate. Inconsistencies in the data obtained will be resolved by agreement between the reviewers after reviewing the full-text article. When

discrepancies occur, an adjudicator will be contacted. If the data published is incomplete or vague, the authors of the research will be contacted. Data extraction will be independently cross-checked.

Quality and Risk of bias assessment:

Two reviewers will independently review each selected article to eliminate bias. All selected articles will be evaluated for their quality based on the Cochrane Collaboration's Risk of Bias Tool 2.0 (RoB 2.0)⁴⁸ for risk of bias assessment across five domains. Assessments will be carried out using an iterative online form available.⁴⁹ The domain of missing outcome data will be evaluated, as per Akobeng and Ebrahim.⁵⁰⁻⁵¹ For each domain, the probability of bias will be evaluated as 'low risk', 'some concerns', or 'high risk'. If at least one area is listed as 'high risk,' studies will be deemed to have an overall high risk of bias. Quality of evidence will be measured using the GRADE rating system.⁵² Publication bias will be evaluated using visual inspection of funnel plot asymmetry.⁵³

Data synthesis Strategy: Meta-analysis:

We will primarily examine the training effect (aerobic, resistance, and concurrent exercise training) on HRV. We will also explore possible sources of heterogeneity among studies by examining aerobic, resistance, and concurrent exercise impact with time point. To attain the standardized mean difference and 95% confidence interval, the data of interest given as continuous will be used for meta-analysis. The Q-statistic and I^2 tests will be used to test for heterogeneity between the included studies. Heterogeneity will be considered low if I^2 is \leq 40%, and high if I^2 is \geq 75%. We will use a random-effects model for meta-analysis if

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226 substantial heterogeneity ($I^2 > 40\%$) or fixed effects for homogeneous effects ($I^2 < 40\%$).⁵⁴
227 Aggregate data obtained from the included studies will be used for quantitative synthesis.
228 By plotting the data on a forest plot, heterogeneity will be evaluated visually.⁵⁵

229 **Analysis of subgroups or subsets:**

230 The sub-analysis will include baseline participant characteristics and exercise intervention
231 characteristics. Interaction effects between variables will be identified for subgroup
232 analysis.⁵⁵

233 **Significance:**

234 Due to modernization and mechanization of lifestyle, there is an increase in overweight and
235 obesity globally. Exercise is a key element to prevent lifestyle disease, therefore it is
236 important to explore dose-response benefits specifically towards heart rate variability to
237 maximize the physiological benefits. The study would help to understand the autonomic
238 response of the heart (i.e., heart rate variability) at different doses of exercise training. Also
239 can help to recommend the training regimen for overweight and obese people for optimum
240 gain in heart rate variability

241 **Ethics and dissemination:**

242 This review will not require an ethical authorization, since participant privacy issues do not
243 exist. Our results will provide data on the various forms of exercise dose-response on the
244 HRV in overweight and obese people. The results of this study will be published in a peer-
245 reviewed international journal, displayed at relevant conferences, and disseminated to
246 obesity-focused public organizations.

247

248 Patient and Public Involvement:

249 No patient involved

250 Contributors:

251 SMK, KV, MA and MGA conceived of the study and provided guidance for drafting the
252 protocol. MA and SMK designed the search strategy. SMK, KV, MA, KNS, SNR and MGA
253 drafted and reviewed the final version systematic review protocol manuscript for
254 submission. All the contributors read and approved the final manuscript.

255 **Funding:** none

256 **Competing interests:** None

257 **Patient consent for publication:** not required

258 **Availability of data and materials:** For this study, data sharing is not applicable.

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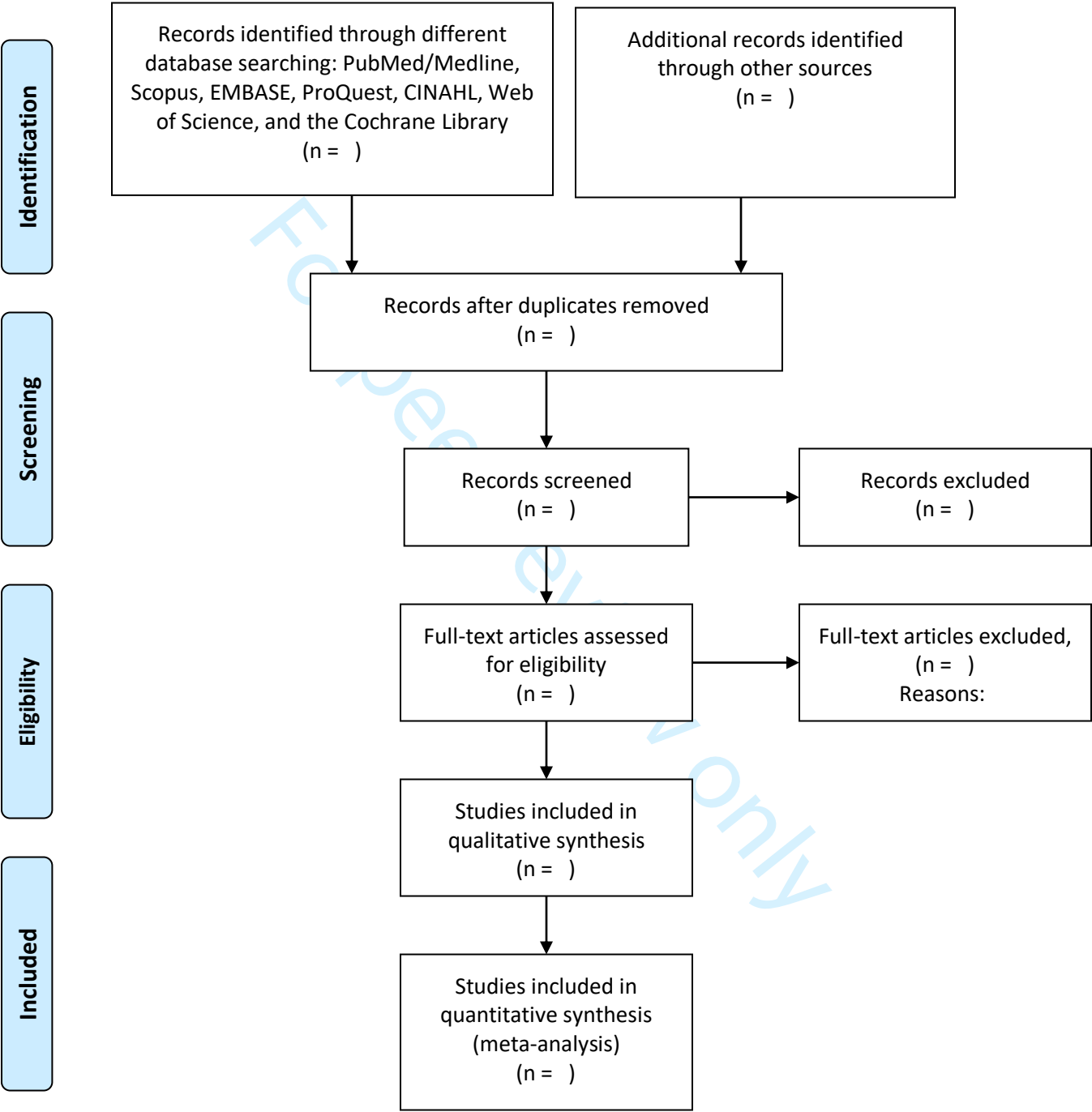
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For peer review only



Figure 1: Flow diagram for study selection based on the PRISMA guidelines: (Moher, Liberati, Tetzlaff, & Altman, 2009)



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Reporting checklist for protocol of a systematic review.

Title: Exercise dose-response relationship with heart rate variability in individuals with overweight and obesity: Protocol for a systematic review and meta-analysis of randomized controlled trials

Based on the PRISMA-P guidelines.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	NA
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1 & 2
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	14
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important	NA

protocol amendments

Sources	#5a	Indicate sources of financial or other support for the review	14
Sponsor	#5b	Provide name for the review funder and / or sponsor	NA
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	NA
Rationale	#6	Describe the rationale for the review in the context of what is already known	3-5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5-9
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5-9
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5-7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9-10
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10-12
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	10-11

1	Outcomes and	#13	List and define all outcomes for which data will be sought,	10-11
2	prioritization		including prioritization of main and additional outcomes, with	
3			rationale	
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5				
6	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of	12
7	individual studies		individual studies, including whether this will be done at the	
8			outcome or study level, or both; state how this information will	
9			be used in data synthesis	
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13	Data synthesis	#15a	Describe criteria under which study data will be quantitatively	12-13
14			synthesized	
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17		#15b	If data are appropriate for quantitative synthesis, describe	12-13
18			planned summary measures, methods of handling data and	
19			methods of combining data from studies, including any	
20			planned exploration of consistency (such as I ² , Kendall's τ)	
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24		#15c	Describe any proposed additional analyses (such as	13
25			sensitivity or subgroup analyses, meta-regression)	
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28		#15d	If quantitative synthesis is not appropriate, describe the type	12-13
29			of summary planned	
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31	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as	12
32			publication bias across studies, selective reporting within	
33			studies)	
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37	Confidence in	#17	Describe how the strength of the body of evidence will be	12
38	cumulative		assessed (such as GRADE)	
39	evidence			
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BMJ Open

Exercise dose-response relationship with heart rate variability in individuals with overweight and obesity: Protocol for a systematic review and meta-analysis of randomized controlled trials

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Title: Exercise dose-response relationship with heart rate variability in individuals with overweight and obesity: Protocol for a systematic review and meta-analysis of randomized controlled trials

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Title: Exercise dose-response relationship with heart rate variability in individuals with overweight and obesity: Protocol for a systematic review and meta-analysis of randomized controlled trials

Abstract:

Introduction: Obesity is a chronic relapsing disease process and serious public health concern that can lead to chronic diseases, medical complications, and a higher risk of disability. Another significant feature of obesity is dysfunction in cardiac autonomic function, which leads to changes in parasympathetic and sympathetic regulation, which can be measured using heart rate variability. The objective of this review is to estimate the extent to which exercise doses impacts on heart rate variability (HRV) among individuals living with overweight and obesity class I and II.

Methods and analysis: A systematic literature search will be performed using PubMed/Medline, Scopus, EMBASE, ProQuest, CINAHL, Web of Science, and the Cochrane Library for articles dating from 1965 to December 2021. Inclusion criteria include studies designed as parallel-arm randomized trials, enrolling adolescent and adult individuals with overweight [BMI $\geq 25 - \leq 29.9$] and obesity [class I BMI: 30 - 34.9 and class II BMI: 35 - 39.9] undergoing aerobic or resistance training or concurrent exercise training. For data synthesis,

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3 55 sensitivity analysis, subgroup analysis, and risk of bias assessment, Stata V.13.0 software will
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6 56 be used.
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9 57 **Ethics and dissemination:** Formal ethical approval is not required. This systematic review
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11 58 will be submitted to a peer-reviewed journal.
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14 59 **Key words:** cardiac autonomic function, heart rate variability, exercise training, aerobic
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17 60 exercise, resistance exercise, concurrent exercise, physical activity
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20 61 **PROSPERO Registry no:** CRD42019104154
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23 62 **Strength and limitation:**
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26 63 ▪ Strength of the design is the focus on dose-response analysis of intervention
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28 64 ▪ Two reviewers will perform data extraction and risk of bias evaluation separately
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31 65 ▪ Only English language article will be included
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34 66 **Introduction:**
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37 67 Over the past 35 years, the global prevalence of obesity has tripled and current trends, if
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39 68 extrapolated would lead to approximately over one billion people by 2030.¹⁻² Individuals
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42 69 living with obesity have a significantly higher risk of developing cardiovascular disease,
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44 70 diabetes, hypertension, cancer, stroke, and chronic disease, including osteoarthritis.¹
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47 71 Obesity has also been linked to alteration in cardiac autonomic activity as seen when
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49 72 measuring heart rate variability (HRV).³⁻⁴ Heart rate variability is a non-invasive technique
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52 73 for analyzing autonomic function by measuring beat-to-beat changes in R-R intervals of
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54 74 electrocardiogram (ECG) signals.⁵ Low HRV is associated with higher skinfold thickness,
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57 75 higher body mass index (BMI), higher body fat percentages and is an autonomous predictor
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59 76 of cardiovascular mortality and sudden cardiac death.⁶⁻⁸ In contrast, higher HRV is found to
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77 be associated with reduced morbidity, mortality, improved quality of life, and psychological
78 well-being.⁹⁻¹¹

79 Earlier studies have reported that obese individuals are relatively more susceptible to
80 ventricular arrhythmias, which has been found to be a powerful indicator of sudden
81 death.¹²⁻¹⁵ Several researchers have shown decreased HRV in obese people (BMI ≥ 30) and
82 this suggests that autonomic disturbances could be involved in the processes stimulating
83 arrhythmia in such people.¹⁶⁻¹⁸ Weight loss by exercise training and dietary intervention, on
84 the other hand, has been shown to reverse the detrimental impact of weight gain on
85 autonomic function.^{6-7,18-19}

86 Benefits of exercise training are documented as a possible non-pharmacological weight-loss
87 approach.^{20,21} All forms of exercise, whether aerobic, resistance, or combination of aerobic
88 and resistance (concurrent), are effective methods of improving anthropometric indicators
89 of adiposity.²²⁻²⁴ These exercise types are characterized by multiple sub-divisions such as
90 frequency, intensity, and volume of exercise that may be considered to constitute the
91 exercise "dosage." The effectiveness of the exercise intervention in reducing body weight is
92 documented as dose-dependent and it is mediated by autonomic control.²⁵⁻²⁹

93 Current evidence on the influence of long-term exercise training on HRV in healthy or obese
94 individuals is inconsistent, with several studies showing significant increase in the HRV
95 following an exercise training with varying dose ranging from 3 weeks to 12 months of
96 exercise training in healthy and obese individuals^{7,19,30-33} while other studies did not show
97 such an effect.³⁴⁻³⁶ Such differences in effect may be due to either participant attributes, a
98 technique of measurement to estimate HRV, study design, exercise types, and/or exercise
99 dose parameter.³⁶

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3 100 A meta-analysis done using data from studies carried out in healthy people suggested that
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6 101 aerobic exercise training can make substantial improvements in the RR interval, and the
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8 102 effect size for changes in the RR interval recorded in this study was significantly higher in
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10 103 long exercise interventions (>12 weeks) than in shorter treatments (<12 weeks).²⁹ Meta-
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13 104 analysis including studies done in the elderly ³⁷ suggested endurance-type exercise is
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15 105 effective for increasing HRV, and exercise frequency appears to be a powerful component of
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18 106 training that leads to HRV improvement.
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21 107 A recent meta-analysis¹⁹ reported improvement in HRV following weight-loss strategies such
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23 108 as dietary approaches, aerobic training, strength training, and exercise programs coupled
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26 109 with dietary approaches. Also, this study suggested that the impact of weight loss on the
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28 110 ANS might depend primarily on the amount of weight loss. Differences in the dosage of
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31 111 exercise, such as the duration, frequency, and strength of exercise training, are considered
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33 112 to be responsible for the degree of improvement in autonomic cardiac function and the
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36 113 change in body weight.¹⁹
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39 114 The Exercise-based weight loss programs are known to be a key part of therapy for obesity
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41 115 and evaluating its impact on HRV would add value to current assessments of the evidence
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44 116 base. In addition, no studies to date have comprehensively analyzed and examined the
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46 117 evidence of exercise dose-response on HRV in people with overweight or obesity. Therefore,
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48 118 the objective of this review is to estimate the extent to which exercise-dose increases heart
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51 119 rate variability in individuals living with overweight and obesity class I and II.
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54 120 **METHODS:**

57 121 **Patient and Public Involvement:**

122 No patient involved as it is a systematic review. The results will be disseminated by the
 123 publication of the manuscript in a peer-reviewed journal.

124 The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-
 125 P) guidelines are used for the current study. PRISMA will be used to assist reporting of the
 126 SR, once completed.³⁸ This systematic review will consider only randomized controlled trials
 127 (RCTs). This systematic review is registered with PROSPERO (CRD42019104154). Any
 128 amendments to this study protocol will be reported.

129 **Electronic Search:**

130 Seven databases will be searched; PubMed/Medline, Scopus, EMBASE, ProQuest, CINAHL,
 131 Web of Science, and the Cochrane Library, for articles dating from 1965 to December 2021,
 132 since Hon and Lee⁵ published their understanding of the clinical importance of heart rate
 133 variability in 1965. We will also refer to clinicaltrials.gov, the World Health Organization's
 134 registry platform ICTRP, the reference lists of key articles identified via Scopus, and articles
 135 that cited the included articles. Also, authors will be contacted to obtain for studies that
 136 have been completed but not published. If more than one publication describes the same
 137 study, the one that provides the most data will be included in the meta-analysis. Studies will
 138 be limited to publications in the English language. The search will be carried out by the first
 139 author and a medical librarian. Table 1 Shows the search strategy for PubMed.

140 **Table 1 Shows the search strategy for PubMed**

(((((((((((((((("exercise"[MeSH Terms]) OR exercise) OR exercise[Text Word]) OR exercise[Title]) OR exercise[Title/Abstract])) OR (((aerobic exercise) OR aerobic exercise[Text Word]) OR aerobic exercise[Title]) OR aerobic exercise[Title/Abstract])) OR
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(((((resistance exercise) OR resistance exercise[Text Word]) OR resistance exercise[Title])
OR resistance exercise[Title/Abstract])) OR (((concurrent exercise) OR concurrent
exercise[Text Word]) OR concurrent exercise[Title]) OR concurrent
exercise[Title/Abstract])) OR (((combination exercise) OR combination exercise[Text
Word]) OR combination exercise[Title]) OR combination exercise[Title/Abstract])) OR
((((("resistance training"[MeSH Terms]) OR resistance training) OR resistance training[Text
Word]) OR resistance training[Title]) OR resistance training[Title/Abstract])) OR (((aerobic
training) OR aerobic training[Text Word]) OR aerobic training[Title]) OR aerobic
training[Title/Abstract])) exercise dose OR dose response OR aerobic dose OR resistance
dose OR concurrent dose OR combination dose OR (((("cardiorespiratory fitness"[MeSH
Terms]) OR cardiorespiratory fitness[Text Word]) OR cardiorespiratory fitness[Title]) OR
cardiorespiratory fitness[Title/Abstract]) OR cardiorespiratory fitness)) OR (((physical
activity) OR physical activity[Text Word]) OR physical activity[Title]) OR physical
activity[Title/Abstract])) OR (((cardiorespiratory endurance) OR cardiorespiratory
endurance[Text Word]) OR cardiorespiratory endurance[Title]) OR cardiorespiratory
endurance[Title/Abstract])) OR (((strength training) OR strength training[Text Word]) OR
strength training[Title]) OR strength training[Title/Abstract])) OR (((strengthening) OR
strengthening[Text Word]) OR strengthening[Title]) OR strengthening[Title/Abstract]))
AND
(((((((("overweight"[MeSH Terms]) OR overweight) OR overweight[Text Word]) OR
overweight[Title]) OR overweight[Title/Abstract])) OR (((("obesity"[MeSH Terms]) OR
obesity) OR obesity[Text Word]) OR obesity[Title]) OR obesity[Title/Abstract])) OR

(((healthy individuals[Text Word]) OR healthy individuals[Title]) OR healthy individuals[Title/Abstract]) OR healthy individuals)))

AND

(((((heart rate variability) OR heart rate variability[Text Word]) OR heart rate variability[Title]) OR heart rate variability[Title/Abstract])) OR (((autonomic function) OR autonomic function[Text Word]) OR autonomic function[Title]) OR autonomic function[Title/Abstract])) OR (((sympathetic function) OR sympathetic function[Text Word]) OR sympathetic function[Title]) OR sympathetic function[Title/Abstract])) OR (((parasympathetic function) OR parasympathetic function[Text Word]) OR parasympathetic function[Title]) OR parasympathetic function[Title/Abstract])) OR (((vagal function) OR vagal function[Text Word]) OR vagal function[Title]) OR vagal function[Title/Abstract]))

Eligibility Criteria and Study selection:

The titles and abstracts screening will be done for eligibility and the article considered appropriate will be reviewed in full-text papers. This process will be conducted using Covidence (www.covidence.org)³⁹ and it is expected to be completed by December 2021.

Inclusion Criteria:

Studies will be included if they report data from a) parallel-arm randomized trials (RCTs), b) enrolled adolescent (Age ≥ 10 years) and adult individuals with overweight [BMI ≥ 25 – ≤ 29.9] and obesity [class I BMI: 30 - 34.9 and class II BMI: 35 - 39.9] undergoing aerobic or resistance exercise training or concurrent exercise training (Table 2)⁴⁰

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Table 2: Operational definitions of exercises type used for the current systematic review according to The American College of Sports Medicine.⁴⁰

Exercise Type	Operational definition
Aerobic/endurance exercise training-	Aerobic exercise as any activity that uses large muscle groups, can be maintained continuously and is rhythmic in nature
Resistance/strength exercise training	Strength training that involves the performance of physical exercises which are designed to improve muscle strength and endurance
Concurrent exercise training	The combination of muscle strength and aerobic exercise during the same session or training program

and had an outcome of interest as HRV c) exercise intervention is reported in terms of frequency, intensity, time, and type, and d) measurement of at least one variable of HRV before and after the training intervention is reported.

Exclusion Criteria:

Exclusion criteria will be a) observational studies, b) studies measuring acute exercise effects, c) obesity class III (BMI ≥ 40) as it has been found that individuals living with severe obesity may have impaired autonomic function and this would confound the outcome of interest, and d) studies including individuals with cardiac, neurodegenerative, kidney or metabolic disease as they have an impact on autonomic function.^{37,41-42}

Study Selection:

Following different database searches, retrieved articles will be imported to the Covidence platform³⁹ where the results will be combined and duplicates will be removed. As a large

number of papers are expected to require screening, four authors will be involved in screening. These authors will also perform pilot-testing of eligibility criteria on the first 10% of titles and abstracts. To harmonize the screening process, a training session will be provided to all reviewers. During this session reviewer will be asked to pilot-screen 15 titles/abstracts to prompt clarifications and screening decisions will be taken in compliance with inclusion/exclusion criteria. After scanning for titles and abstracts, articles that do not meet the inclusion requirements will be excluded and the remaining articles will have their full-text versions retrieved. The full-text screening will be done by two lead members of the synthesis team using the level of agreement between reviewers. Kappa statistics will be used to test the agreement [i.e. thresholds: <0.20 slight agreement, 0.21 - 0.40 fair agreement, 0.41 - 0.60 moderate agreement, 0.61 - 0.80 substantial agreement and >0.80 almost perfect agreement].⁴³ Disputes will be settled by agreement with the reviewers or by contacting an adjudicator. In a PRISMA flow chart, the study selection process is displayed.⁴⁴(Figure I)

Data extraction and analysis:

Outcomes:

In this study, the primary outcome of interest is the time domain (SDNN, SDANN, RMSSD, pNN50) and frequency domain variables of HRV (Total power, VLF, LF, HF, LF/HF ratio). (Table 3)

Table 3: Heart rate variability Domains.⁵

Secondary outcomes include Cardiorespiratory endurance, muscular strength, adiposity/anthropometric measures. These outcomes are chosen based on the previous research.^{7,19,30-33} If data are available in qualifying studies, the relationship of exercise training with other endpoints, such as time effect and interaction effect with sociodemographic variables, anthropometric measures, presence of cardiovascular risk factors, diet, exercise adherence, and life stress, will also be analyzed.

Data extraction:

Time domain measures of HRV: Variable(units) and description	
SDNN (ms)	Standard deviation of all NN intervals
SDANN (ms)	Standard deviation of the averages of NN intervals
RMSSD (ms)	The square root of the mean of the sum of the squares of differences between adjacent NN intervals
pNN50 %	NN50 count divided by the total number of all NN intervals
Frequency domain measures of HRV: Variable(units) and description	
Total power ms ²	The variation of NN intervals over the temporal segment
VLF (ms ²)	Power in very low frequency range
LF (ms ²)	Power in low frequency range
HF (ms ²)	Power in high frequency range
LF/HF ratio	Ratio of LF and HF

A data extraction form will be adopted from published literature.⁴⁵⁻⁴⁷ Data extraction process consists of manuscript title, author, time of publication, source of literature, characteristics of the trial (author, conducted/ publication year, duration, place of the trial conducted, number of participating centers, study design), the participants (sample size, participants randomized and patients analyzed in each group, age, sex, socioeconomic status, height, weight, body mass index, waist circumference, waist-hip ratio, waist-height

ratio, and body fat percent), intervention (aerobic, resistance, and concurrent exercise dose in terms of frequency, intensity, number of sessions, duration, and progression), control group treatment, method of randomization, method of allocation, blinding process, outcome time point and follow-up period, lack of follow-up or withdrawal, any incidental findings reported and the main outcome measurement heart rate variability reported either in absolute or log transformed or both. Two independent reviewers will pilot test the data extraction form and to resolve any disagreements team meetings will be conducted to refine the form. The two reviewers will perform data extraction separately. A training session will be held to harmonize the extraction of data, and at least two pilot extractions will be carried out to ensure accuracy. A written 'Data Extraction Guide' with detailed instructions will also be provided to reviewers. To assure accuracy, one lead member of the systematic review team will extract data from each article. An impartial third reviewer will cross-check the data extracted in duplicate. Inconsistencies in the data obtained will be resolved by agreement between the reviewers after reviewing the full-text article. When discrepancies occur, an adjudicator will be contacted. If the data published is incomplete or vague, the authors of the research will be contacted. Data extraction will be independently cross-checked.

Quality and Risk of bias assessment:

Two reviewers will independently review each selected article to eliminate bias. All selected articles will be evaluated for their quality based on the Cochrane Collaboration's Risk of Bias Tool 2.0 (RoB 2.0)⁴⁸ for risk of bias assessment across five domains. Assessments will be carried out using an iterative online form available.⁴⁹ The domain of missing outcome data will be evaluated, as per Akobeng and Ebrahim.⁵⁰⁻⁵¹ For each domain, the probability of

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3 224 bias will be evaluated as 'low risk', 'some concerns', or 'high risk'. If at least one area is listed
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6 225 as 'high risk,' studies will be deemed to have an overall high risk of bias. Quality of evidence
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8 226 will be measured using the GRADE rating system.⁵² Publication bias will be evaluated using
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10 227 visual inspection of funnel plot asymmetry.⁵³
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17 229 **Data synthesis Strategy: Meta-analysis:**
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20 230 We will primarily examine the training effect (aerobic, resistance, and concurrent exercise
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22 231 training) on HRV. We will also explore possible sources of heterogeneity among studies by
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24 232 examining aerobic, resistance, and concurrent exercise impact with time point. To attain the
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26 233 standardized mean difference and 95% confidence interval, the data of interest given as
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28 234 continuous will be used for meta-analysis. The Q-statistic and I^2 tests will be used to test for
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30 235 heterogeneity between the included studies. Heterogeneity will be considered low if $I^2 \leq$
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32 236 40%, and high if $I^2 \geq 75\%$. We will use a random-effects model for meta-analysis if
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34 237 substantial heterogeneity ($I^2 > 40\%$) or fixed effects for homogeneous effects ($I^2 < 40\%$).⁵⁴
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36 238 Aggregate data obtained from the included studies will be used for quantitative synthesis.
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38 239 By plotting the data on a forest plot, heterogeneity will be evaluated visually.⁵⁵
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45 240 **Analysis of subgroups or subsets:**
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48 241 The sub-analysis will include baseline participant characteristics and exercise intervention
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50 242 characteristics. Interaction effects between variables will be identified for subgroup
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52 243 analysis.⁵⁵
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56 244 **Significance:**
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Due to modernization and mechanization of lifestyle, there is an increase in overweight and obesity globally. Exercise is a key element to prevent lifestyle disease, therefore it is important to explore dose-response benefits specifically towards heart rate variability to maximize the physiological benefits. The study would help to understand the autonomic response of the heart (i.e., heart rate variability) at different doses of exercise training. Also can help to recommend the training regimen for overweight and obese people for optimum gain in heart rate variability

Ethics and dissemination:

This review will not require an ethical authorization, since participant privacy issues do not exist. Our results will provide data on the various forms of exercise dose-response on the HRV in overweight and obese people. The results of this study will be published in a peer-reviewed international journal, displayed at relevant conferences, and disseminated to obesity-focused public organizations.

Contributors:

SMK, KV, MA and MGA conceived of the study and provided guidance for drafting the protocol. MA and SMK designed the search strategy. SMK, KV, MA, KNS, SNR and MGA drafted and reviewed the final version systematic review protocol manuscript for submission. All the contributors read and approved the final manuscript.

Funding: none

Competing interests: None

Patient consent for publication: not required

Availability of data and materials: For this study, data sharing is not applicable.

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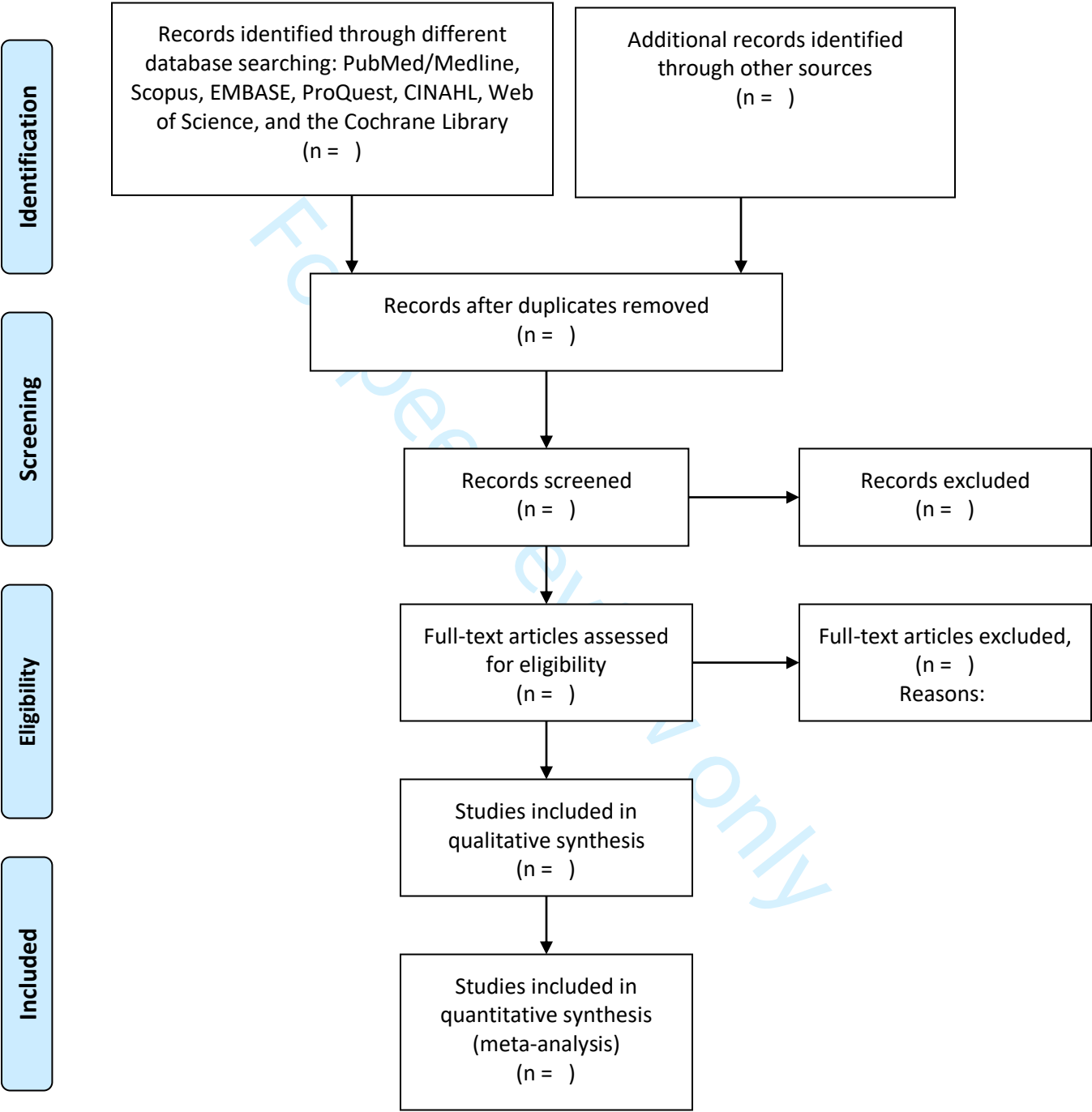
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Figure 1: Flow diagram for study selection based on the PRISMA guidelines: (Moher, Liberati, Tetzlaff, & Altman, 2009)



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From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Reporting checklist for protocol of a systematic review.

Title: Exercise dose-response relationship with heart rate variability in individuals with overweight and obesity: Protocol for a systematic review and meta-analysis of randomized controlled trials

Based on the PRISMA-P guidelines.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	NA
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1 & 2
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	14
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important	NA

protocol amendments

Sources	#5a	Indicate sources of financial or other support for the review	14
Sponsor	#5b	Provide name for the review funder and / or sponsor	NA
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	NA
Rationale	#6	Describe the rationale for the review in the context of what is already known	3-5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5-9
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5-9
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5-7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9-10
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10-12
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	10-11

1	Outcomes and	#13	List and define all outcomes for which data will be sought,	10-11
2	prioritization		including prioritization of main and additional outcomes, with	
3			rationale	
4				
5				
6	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of	12
7	individual studies		individual studies, including whether this will be done at the	
8			outcome or study level, or both; state how this information will	
9			be used in data synthesis	
10				
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12				
13	Data synthesis	#15a	Describe criteria under which study data will be quantitatively	12-13
14			synthesized	
15				
16				
17		#15b	If data are appropriate for quantitative synthesis, describe	12-13
18			planned summary measures, methods of handling data and	
19			methods of combining data from studies, including any	
20			planned exploration of consistency (such as I ² , Kendall's τ)	
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23				
24		#15c	Describe any proposed additional analyses (such as	13
25			sensitivity or subgroup analyses, meta-regression)	
26				
27				
28		#15d	If quantitative synthesis is not appropriate, describe the type	12-13
29			of summary planned	
30				
31	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as	12
32			publication bias across studies, selective reporting within	
33			studies)	
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37	Confidence in	#17	Describe how the strength of the body of evidence will be	12
38	cumulative		assessed (such as GRADE)	
39	evidence			
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